Mercury induced immune complex glomerulopathy. An experimental study.

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Summary

Subject of this thesis is the development of an experimental model for immune complex glomerulopathy, induced by inorganic mercury.

Inorganic mercury has been used in the past for the treatment of tuberculosis and syphilis. It has also been employed as a diuretic and in teething powders. Mercury is still frequently used in antiseptic ointments and in skin-lightening creams.

Proteinuria and a nephrotic syndrome associated with membranous glomerulopathy (MGP) in man have been recognized for a long time as one of the complications of exposition to low doses of mercury. This form of immune complex glomerulopathy, characterized by the presence of immune aggregates along the epithelial side of the glomerular basement membrane (GBM) can also be seen in patients treated with other drugs (gold, penicillamine, captopril).

The way the glomerulopathy is induced by mercury and the other drugs is unclear, the more since the pathogenetic antigen is unknown. Experimental studies of mercury-induced immune complex glomerulopathy have not succeeded in identifying the pathogenetic antigen sofar. The idea, that mercury would cause tubular cell damage, resulting in an anti-tubular brushborder antibody response could not be confirmed by these experimental studies.

The purpose of this study was to investigate pathogenetic mechanisms in mercury-induced immune complex glomerulopathy in the PVG/c rat, a high responder in the induction of autologous immune complex glomerulonephritis.

Chapter 1 describes the induction of the glomerulopathy. Administration of low doses of $HgCl_2$, three times a week, results after about twelve weeks in the development of IgG containing immune aggregates in a granular pattern along the GBM and in the mesangium. Other immunoglobulins and complement are not found in the aggregates. Proteinuria is absent. Coinciding with the appearance of glomerular immune aggregates, circulating antinuclear antibodies (ANA) are found in the sera of the mercury injected rats. Acid eluates of the glomeruli contain ANA as well, suggesting ANA to be present in the glomerular immune aggregates.

Administration of a single dose of complete Freund's adjuvant at the start of the mercury injections accelerates the development of ANA and glomerular immune complex aggregates with approximately 4 weeks.

In chapter 2, the identification of the nuclear antigen is described, to which mercury elicits an antibody response. This antigen is shown to be a con A binding glycoprotein from the non-histon chromatin fraction.

In chapter 3, the mechanism of glomerular immune aggregate formation is studied. Using *ex vivo* perfusions and *in vitro* incubations, antinuclear antibodies belonging to the IgG serum fraction of mercury injected animals are shown to bind to normal rat GBM. Binding is not obtained, when the antinuclear antibodies are absorbed with purified nuclei. These results suggest, that antinuclear antibodies bind to or cross-react with antigenic sites in the GBM.

Aspects of cellular immunity and immunoregulation in mercury diseased rats are described in chapter 4. Lymphocytes from mercury injected rats are found to be sensitized for nuclear and Fx1A antigens, when studied in a direct migration inhibition assay, but the lymphocytes show a decreased mitogenic response to phytohaemagglutinin as compared with lymphocytes from control animals.

Con A-activated suppression, assessed in a co-culture system, is decreased in lymphocytes from mercury diseased animals compared to the suppressive activity, generated by con A in lymphocytes from control rats. Mercury administration to PVG/c rats after neonatal thymectomy is found to result much earlier in the development of antinuclear antibodies and glomerular immune aggregates than in non-thymectomized control animals. This effect is not seen after adult thymectomy.

From these results it is concluded, that mercury-induced antibody responses are associated with cell-mediated immune reactions and with a disturbance of the immunoregulation. Whether or not these phenomena are involved in the pathogenesis of the disease, remains to be elucidated.

In chapter 5, this issue and the results of the previous chapters are discussed. The differences with other models of mercury-induced immune complex glomerulopathy are reviewed. So is the role of circulating immune complexes as to the origin of vascular and mesangial immune deposits. The binding of antinuclear antibodies to the GBM is compared with corresponding findings in man and the similarity in binding capacity between mercury-induced ANA, anti-Fx1A antibodies and con A is discussed. The origin of the antinuclear antibody response is related to

possible nuclear damage or to the changes in the immunoregulation, as described in chapter 4.

The model offers an opportunity to investigate further the relation between immunodysregulation, autoantibodies and the pathogenesis of immune complex glomerulopathy, a relation which is thoroughly studied in human pathology as well.